Nevirapine and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis

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Objective: To draw attention to the many cases of Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) related to nevirapine detected in a multinational case–control study of SJS and TEN.

Methods: Actively detected cases and matched hospital controls were interviewed for exposure to drugs and other risk factors. Data were analysed with case–control and case-crossover methods.

Results: Between May 1997 and November 1999, a diagnosis of SJS or TEN was established in 246 patients. Eighteen were known to be infected by HIV-1 (7.3%), 15 out of these 18 had been exposed to nevirapine. The reaction began 10–240 days after the introduction of nevirapine (median, 12 days) and all patients had received escalating doses. In 10 patients the reaction occurred with the initial dosage. All but one patients received simultaneously a variety of other antiretroviral agents but no specific drug combination emerged, and nevirapine was the only drug significantly associated with an increased risk of SJS or TEN in HIV-infected persons [odds ratio, 62 (10.4; $^{+}\infty$) in the case–control analysis; odds ratio, $^{+}\infty$ (2.8; $^{+}\infty$) in the case-crossover analysis].

Conclusions: In European countries the risk of SJS or TEN in the context of HIV infection appears to be associated with nevirapine. The respect of a lead-in period does not appear to prevent SJS or TEN. Because of the severity of these reactions and the long elimination half-life of nevirapine, we suggest discontinuation of the drug as soon as any eruption occurs.

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Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous disorders characterized by acute skin blisters and mucous membrane erosions. They are severity variants of drug reactions that result in necrosis of the epidermis and other epithelia. According to current definitions [1] the main difference between the two is the extent of skin detachment: $< 10\%$ for SJS and $> 30\%$ for TEN (Fig. 1).

Because SJS and TEN are very rare, the risk cannot be

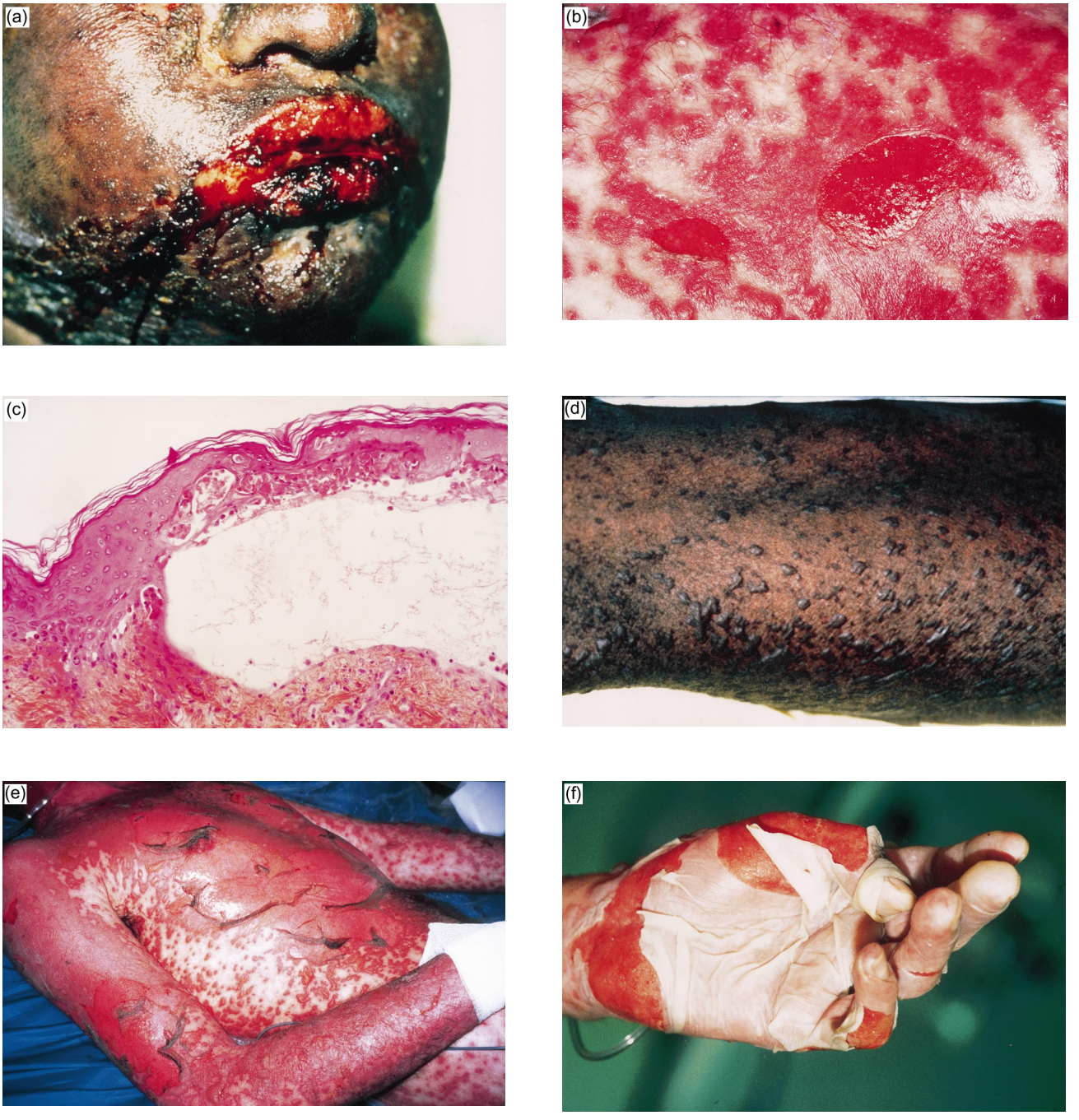

Fig. 1. Clinical examples of SJS and TEN cases related to Nevirapine. (a) Erosions of lips and mouth are characteristics of SJS and TEN. (b) Magnification of cutaneous lesions showing purpuric macules, small blisters and positive Nikolski, i.e. detachment of epidermis on pressure. (c) Skin biopsy showing the detachment of necrotic epidermis. (d) SJS with discrete non-confluent small blisters, involving $< 10\%$ of the body surface area. (e) Coexistence of small blisters and detachment of the epidermis on 35–40% of the body surface area in TEN. (f) Detachment of the epidermis is frequent on palms and soles.

evaluated in cohorts of treated patients and case–control studies are considered to be more accurate. To assess the risk of SJS or TEN in the context of drug treatment we have been conducting, since May 1997, a case–control study in Austria, France, Germany, Holland, Italy and Israel (EuroSCAR study). Risks are evaluated by comparing the rates of exposure to drugs between case patients and the controls. We present here the data collected in HIV-infected patients enrolled in that study up to 1 November 1999.

Patients and methods

Cases of SJS and TEN were actively detected through regular contact with a network of relevant facilities at which cases were treated. All cases requiring hospital admission were included. The detection network covered a population of about 120 million.

Cases

Selection criteria were: hospitalization with a diagnosis of SJS or TEN; widespread exanthema with $\geqslant 1\%$ detachment; more than one blister; not only acral extension; presence of mucous membrane erosions. Potential cases were interviewed by trained investigators to determine exposure to drugs in the 4 weeks before admission (or before the onset of the disease in cases occurring within a hospital).

Clinical data, clinical photographs (available in 90% of cases) and skin biopsies (available in 70% of cases) of potential cases were reviewed by experts blinded to drug exposure data and who: ascertained potential cases as definite, probable, possible or excluded; classified the cases as SJS (detachment $< 10\%$ of the body surface area), overlap SJS–TEN (detachment 10–29%) or TEN (detachment $\geqslant 30\%$); and determined the most probable date of onset (index date). Only patients with a definite or probable diagnosis were included in the study.

Hospital controls

Three hospital controls matched for age and sex were obtained for each case among persons admitted to the same hospital with conditions which were not expected to result from drug use (e.g. trauma, pneumonia, appendicitis, hernia).

Questionnaire

Standardized information was obtained from cases and controls concerning medications, recent infections, demographics and relevant medical history. Data collection on medications used a list of indications (e.g., pain, headache, cough) and a list of trade-names of the main 'suspect' drugs.

Analyses

Clinical characteristics and drug exposures before the index date were checked in all patients known to be infected by HIV-1.

Because with standard case–control analysis the crude odds ratio (OR) was 'infinite' for nevirapine, we used exact logistic regression, median unbiased estimate calculated according to Hirji *et al.* [2], and lower limit of the confidence interval according to Thomas [3].

The control group extracted from the general population was not optimal for evaluating drugs only indicated for the treatment of HIV infection. To overcome this limitation we performed a case-crossover analysis. The principle of this analysis is to compare the rate of exposure to a risk factor at different periods of time before the occurrence of an acute event [4,5]. In this study exposures during a 'case period' of 7 days before the index date were compared with exposures in a 'control period' of 7 days, 3–4 weeks earlier. Therefore each case served as his own matched control. The OR was the ratio of cases exposed during the 'risk period' only to cases exposed during the 'control period' only. When the ratio was infinite an exact binomial confidence interval was calculated.

Results

Between May 1997 and November 1999 364 potential cases and 874 potential controls were enrolled. A probable or definite diagnosis of SJS or TEN was established in 246 cases. Among them 18 were known to be infected by HIV-1 (7.3%): three with SJS, seven with SJS/TEN overlap and eight with TEN. Two of 18 died as a result of the reaction. Among the 246 SJS and TEN patients 57 died (23%). Because the study was limited to the acute phase of the disease, information on sequelae was not available.

Recent or recurrent herpes was not associated to the reactions (0/18 and 2/18 respectively versus 6% and 24% of controls.)

Exposure to nevirapine was present in 15 out of 18 patients (83%). The other three patients were respectively exposed to: diclofenac alone; fluconazole and mintezol; amoxicilline + clavulanic acid, allopurinol and efavirenz, all introduced recently, plus clonazepam, cotrimoxazole, stavudine and abacavir for longer than 2 months.

The characteristics of the 15 patients exposed to nevirapine are presented in Table 1. They were four women and 11 men aged 21–59 years (median, 35 yeras), 10 were from France, three were from Ger-

Table 1. Characteristics of patients with Stevens–Johnson syndrome or toxic epidermal necrolysis exposed to nevirapine.

Age (years)	Sex	Country	Diagnosis	Detachment (% of body surface area)	Mucosal involvement	Delay[a]	Nevirapine dose at onset of reaction (mg/day)	CD4 cell count ($\times 10^6$/l)	Other antiretroviral drugs[b]	Other relevant exposure(s)[b]
35	Male	Germany	TEN	55	O	11	400	87	Nelfinavir, didanosine	Aspirin, pentamidine
38	Female	Germany	SJS	4	E, L, O	43	400	1033	Stavudine, didanosine	Paracetamol
35	Male	France	TEN	30	L, O	10	200	300	Zidovudine, ritonavir	
40	Male	France	SJS/TEN	12	L, O, G	17	400	41	Abacavir, nelfinavir, zalcitabine, zidovudine	Cotrimoxazole, azithromycine
23	Male	France	SJS/TEN	17	E, L, O, G	12	200	470	Zidovudine, lamivudine	
48	Male	France	SJS	8	L, O, G	11	200	200	Stavudine	Omeprazole
59	Male	France	SJS/TEN	13	E, L, O, G	31	400	70	Abacavir, didanosine	Cotrimoxazole, fluconazole
33	Male	France	TEN	45	E, L, O, G	11	200	480	Didanosine, stavudine	
34	Male	France	SJS	5	E, L, O	17	200	150	Zidovudine, lamivudine	
26	Female	France	SJS/TEN	25	E, L, O, G	11	200	475	Zidovudine, lamivudine	
24	Female	France	TEN	32	E, L, O, G	10	200	268	Didanosine, stavudine	
50	Male	France	SJS/TEN	28	E, L, O, G	17	200	185	Stavudine, lamivudine	
38	Male	Germany	TEN	32	E, L, O, G	16	200	Unknown	Zidovudine, lamivudine, saquinavir, ritonavir, abacavir	Cotrimoxazole, azithromycine
44	Male	Italy	SJS/TEN	14	L, O, G	240	400	4	None	Fluconazole
21	Female	The Netherlands	TEN	31	E, L, O, G	10	200	778	Zidovudine, indinavir, didanosine	

[a]Time from first intake of nevirapine to onset of erythema (days). [b]A drug name given in italic type indicates long-term (≥ 2 months) exposure. E, Eyes; L, lips; O, oral mucosa; G, genital mucosa.

many, one was from the Netherlands and one was from Italy. The most recent counts of CD4 cells ranged from 4 to 1033 $\times 10^6$/l (median, 234 $\times 10^6$/l). All patients had mucous membrane erosions. The detachment of epidermis involved 4–55% of the body surface area (median, 25%). One patient died from SJS/TEN overlap.

All but one of the 15 patients exposed to nevirapine received other antiretroviral agents, introduced on the same date as nevirapine in 12 cases. No specific drug combination appeared among these associated drugs (stavudine, five; didanosine, five; zidovudine, four; lamivudine, four; abacavir, two; ritonavir, one; nelfinavir, one).

The reaction began 10–240 days after the introduction of nevirapine (median 12 days). All patients had initially received a daily dose of 200 mg (one tablet) according to the recommendation of a lead-in period. For 10 out of 15 patients the reaction began when they were still taking this initial dosage.

As no control among the 676 validated was exposed to nevirapine the OR was infinite, with a median unbiased estimate of 62 and a lower value of the 95% confidence interval of 10.4.

Details of the case-crossover analysis are shown in Table 2. Nevirapine was the only antiretroviral agent significantly associated with an increased risk of SJS or TEN.

We were not able to analyse the effect of treatments (corsticosteroids or high dose human immunoglobulins) given for SJS or TEN because this information was obtained for only a minority of patients.

Discussion

HIV infection increases the risk of drug eruptions [6] including SJS and TEN [7,8]. In a previous case–control study of SJS and TEN in Europe, 7% of patients were HIV infected [8]. In HIV infected patients most cases were related to antibacterial sulphonamides [6,9] in Western countries and to thiacetazone [10] in Africa.

The introduction of highly active antiretroviral therapy (HAART) resulted in a dramatic reduction of opportunistic infections. The lower exposure to antibacterial sulphonamides did not lead to the expected decrease of SJS or TEN in HIV-infected persons. Among cases of SJS and TEN enrolled in this study during the last 3 years, the percentage of patients known to be HIV infected was exactly the same as it was 10–5 years ago

Table 2. Case-crossover analysis.

	Number of patients exposed[a] during			
	Case period only	Control period only	Both periods	Odds ratio (95% CI)
Nevirapine	12	0	3	$^{+}\infty$ [2.8;$^{+}\infty$]
Other NNRTI	1	0	0	$^{+}\infty$ [0;$^{+}\infty$]
Protease inhibitor	0	0	5	n.a.
NRTI[a]	4	0	11	$^{+}\infty$ [0.7;$^{+}\infty$]
Cotrimoxazole	0	0	4	n.a.

[a]The numbers differ from those in Table 1 because patients often took at the same time two drugs belonging to the same category [often two nucleoside reverse transcriptase inhibitors (NRTI)]. NNRTI: Non-nucleoside reverse transcriptase inhibitor; n.a., Not applicable; CI, confidence interval.

[8] (7.3% and 7% respectively). Our data strongly suggest that this persistence of a high risk of SJS or TEN in relation to HIV infection is currently associated with exposure to nevirapine.

The reasons why HIV-infected patients are at increased risk of severe cutaneous reactions are unclear. The mechanisms probably involve drug-specific cytotoxic lymphocytes. Therefore one may suspect that it could be part of an 'immune restoration syndrome'. We consider this hypothesis to be unlikely as in previous years many cases were related to sulfadiazine treatment of central nervous system toxoplasmosis in profoundly immunosuppressed patients. In addition, if these reactions were related to immune restoration they should be observed with a variety of HAART regimens and not be restricted to those including nevirapine.

A high risk of severe cutaneous reactions had been detected in pre-marketing trials of nevirapine, but the benefits of this new antiretroviral agent were considered to outweigh the risk of SJS or TEN. In addition, it was suggested that the observance of a lead-in period decreased the risk of skin reactions [11,12]. However, in two-thirds of the cases exposed to nevirapine in the present study, the reaction occurred during the period of initial low dosage suggesting that escalating doses did not protect against SJS or TEN.

Whether the administration of systemic corticosteroids in addition to nevirapine during the lead-in period might decrease the rate of cutaneous reactions remains unknown [13,14].

Efavirenz and delavirdine, other non-nucleoside reverse transcriptase inhibitors (NNRTI), were released in Europe a few months after nevirapine. These drugs have not been used in as many people as nevirapine. In France at the end of 1999 about 15% of HAART regimens included nevirapine and 10% included efavirenz (D. Costagliola, French Hospital Database on HIV; personnal communication, January 2001). In our study we saw a single case (SJS/TEN overlap) exposed to efavirenz and none exposed to delavirdine. Our data strongly suggest that the risk of SJS or TEN is lower with efavirenz or delavirdine than with nevirapine.

We advise physicians to consider seriously the risk of these life-threatening cutaneous reactions when prescribing a HAART regimen. When nevirapine has advantages over another NNRTI, they must inform their patient of the risk of cutaneous reactions and provide clear guidelines of what to do in the case of skin eruption.

In HIV-infected patients a frequent practice is to 'treat through' mild eruptions and to withdraw the suspected drug only if markers of seriousness are present. Derived from accumulated clinical experience with sulphonamides in pneumocystosis, this attitude was justified by a lower effectiveness of alternative treatments and by the short elimination half-life of sulfamethoxazole. Concerning nevirapine a similar recommendation was issued by the European Agency for the Evaluation of Medicinal products: 'nevirapine must be permanently discontinued in patients developing a serious cutaneous reaction' (EMEA/11260/00, London 12 April 2000).

Withdrawing a drug with a long half-life when signs of a serious cutaneous reaction are already obvious may be too late. Actually the mortality of patients hospitalized for SJS or TEN was not improved if suspected drugs with long half-lives were withdrawn as soon as a diagnosis of SJS or TEN was made [15].

Considering the high risks of severe cutaneous adverse reactions associated with nevirapine; the long elimination half-life of this drug (25–30 h); and the existence of alternative drugs with lower risk of severe skin reactions, we suggest reconsideration of the 'treating through' attitude and recommend withdrawing nevirapine if any cutaneous eruption occurs during the first month of treatment.

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